International Journal of Pharmaceutics 362 (2008) 74–80

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Influence of solid-state acidity on the decomposition of sucrose in amorphous systems (I)

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ARTICLE INFO

Article history:
Received 10 February 2008
Received in revised form 9 May 2008
Accepted 16 June 2008
Available online 4 July 2008

Keywords:
Solid state
Acidity
Amorphous
Sucrose
Decomposition

ABSTRACT

It was of interest to develop a method for solid-state acidity measurements using pH indicators and to correlate this method to the degradation rate of sucrose. Amorphous samples containing lactose 100 mg/ml, sucrose 10 mg/ml, citrate buffer (1–50 mM) and sodium chloride (to adjust the ionic strength) were prepared by freeze-drying. The lyophiles were characterized using powder X-ray diffraction, differential scanning calorimetry and Karl Fischer titremetry. The solid-state acidity of all lyophiles was measured using diffuse reflectance spectroscopy and suitable indicators (thymol blue or bromophenol blue). The prepared lyophiles were subjected to a temperature of 60 °C and were analyzed for degradation using the Trinder kit. The results obtained from this study have shown that the solid-state acidity depends mainly on the molar ratio of the salt and the acid used in buffer preparation and not on the initial pH of the solution. The degradation of sucrose in the lyophiles is extremely sensitive to the solid-state acidity and the ionic strength. Reasonable correlation was obtained between the Hammett acidity function and sucrose degradation rate. The use of cosolvents (in the calibration plots) can provide good correlations with the rate of an acid-catalyzed reaction, sucrose inversion, in amorphous lyophiles.

1. Introduction

It is well known that amorphous solids often have desirable pharmaceutical properties, such as rapid dissolution rates. However, amorphous solids are difficult to develop because of their potential to chemical and physical (crystallization) instabilities (Byrn et al., 1999). Several factors might influence the chemical reactivity in the solid state. Molecular mobility and moisture content are considered to be the major factors that define chemical stability of freeze-dried and other amorphous solids. Recently, medium polarity and acidity are suggested to play significant role in chemical stability. Therefore, the chemical reactivity (Karel and Labuza, 1968; Labuza et al., 1969; Carstensen and Pothisiri, 1975; Flink, 1983; Townsend and Deluca, 1988; Glombitza and Schmidt, 1995; Dublin, 1995; O'brien, 1996; Badawy, 2001; Schebor et al., 1995; Buera et al., 1995; Kouassi and Ross, 2000) and the solid-state acidity (Scheef et al., 1998; Li et al., 2004; Glombitza et al., 1994; Zinchuk et al., 2005) in pharmaceutical solid systems have been the subjects of many investigations. In particular, the Hammett (Hammett, 1935) acidity function, H, is being used to express solid-state acidity:

$$H = \log\left[\frac{c_{A^-}}{c_{HA}}\right] + pK_a = -\log\ a_H + \left[\frac{f_{A^-}}{f_{HA}}\right] \quad (1)$$

where c, f and a_H are the indicator concentration, indicator activity coefficient and proton activity, respectively, K_a is the dissociation constant of the indicator in the standard state, and A^- and HA correspond to deprotonated and protonated indicator species, respectively.

Hammett acidity function was used to describe rate of chemical reactivity in solutions of strong acids and electrolytes (Hammett, 1935) and sucrose inversion in lyophilies (Chatterjee, 2004). Shalaev et al. (2000) tried to explain the degradation behavior of sucrose in the solid state. The authors concluded that sucrose, colyophilized with an acid undergoes significant acid-catalyzed inversion at 50 °C and that the rate of the reaction correlates with the initial solution pH. No attempts were made, in that study, to determine the acid–base characteristics of the citrate buffer after lyophilization.

The purpose of this investigation is to refine a method for solid-state acidity measurements using pH indicators and to correlate this method to the degradation rate of sucrose. One of the potential shortcomings of the Hammett acidity is the use of the dissociation constant in aqueous solution, which does not account for dependence between media properties (e.g., polarity) and

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doi:10.1016/j.ijpharm.2008.06.024

Table 1
Prelyo solutions compositions and the glass transition temperatures (T_g) of the resulting lyophiles

Citric acid:Na citrate weight ratio	Pelyo solutions			Lyophiles		
	Buffer concentration (mM)	Prelyo pH	NaCl (mg/ml)	T_g (°C) 1st run	T_g (°C) 2nd run	Calculated[a]
3.96	1	3.25	0.00	80	81	104
3.96	1	3.25	1.25	79	79	104
3.96	10	2.78	1.15	78	81	93
3.96	50	2.59	0.72	72	73	66
1.96	1	3.34	0.00	81	87	104
1.96	1	3.35	1.24	80	87	104
1.96	10	2.90	1.08	87	91	95
1.96	50	2.79	0.34	79	82	70
1.21	1	3.32	0.00	94	97	104
1.21	1	3.31	1.24	91	92	104
1.21	10	2.92	1.01	91	93	96
1.21	50	2.85	0.00	85	87	73

All samples contained lactose monohydrate (10%, w/v) and sucrose (1%, w/v).
[a] Using Fox equation.

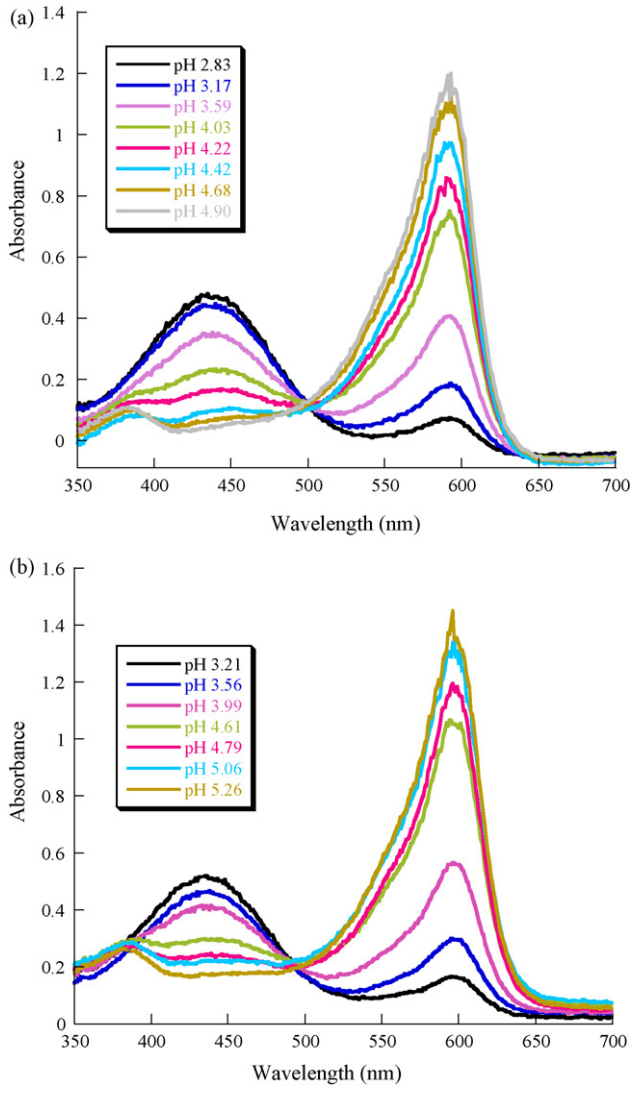

Fig. 1. UV–vis spectra of bromophenol blue in (a) aqueous solutions and (b) in a water–isopropyl alcohol (25%, v/v) mixtures. (For interpretation of the references to colour in this artwork, the reader is referred to the web version of the article.)

spectral properties of the indicators. Therefore, I suggest that the use of cosolvents might provide a better estimate for the Hammett acidity in the lyophiles. To the best of my knowledge, the use of cosolvents to determine the Hammett acidity has not been described in the literature. Also the Hammett acidity–rate profile for the acid-catalyzed sucrose degradation and the role of ionic strength in chemical stability of the lyophiles have not been previously explored.

2. Materials and methods

2.1. Materials

Sodium salts of thymol blue (TB) and bromophenol blue (BB), α-lacotose monohydrate, sucrose >99.5%, anhydrous citric acid and phosphoric acid 85% were all obtained from Sigma–Aldrich Co. (St. Louis, MO, USA). Sodium chloride, potassium phosphate monobasic and dibasic, and sodium citrate dihydrate tribasic were all obtained from Mallinckrodt Baker, Inc. (Phillipsburg, NJ or Paris, KY, USA). Anhydrous sodium dihydrogen citrate was obtained from Fluka Chemie GmbH (Germany). Glucose assay packages were obtained from Diagnostic Chemicals Ltd. (Oxford, CT, USA).

2.2. Methods

2.2.1. Lyophilization

Solutions containing lactose monohydrate (10%, w/v), sucrose (1%, w/v), 1–50 mM sodium citrate buffer, sodium chloride (to adjust the ionic strength to 0.022 M), with an indicator (in case of acidity measurements) or without (in case of kinetic studies) were freeze-dried using a VirTis Advantage freeze-dryer (VirTis Co., Gardiner, NY, USA). Citric acid and sodium citrate were used in different weight ratios in order to yield solutions with pH values ranging from 2.59 to 3.35. Citrate buffer was also used in different concentrations in order to yield solutions with different buffer capacities. In order to investigate the effect of ionic strength, the 1 mM citrate buffers were also prepared without an adjustment for the ionic strength. The pH values of all solutions were measured using a pH meter (Oakton pH 500 Series) which was calibrated using standard buffers. In the freeze-dryer, the solutions were filled in 60-ml glass jars (~15 ml of solution per jar), cooled from room temperature to −40 at 1 °C/min and held for 90 min. Primary drying was carried out at a shelf temperature of −40 °C for 30 h, and −30 °C for 30 h, followed by an increase in the temperature to 0 °C. Secondary drying was carried out at 45 °C for 10 h. The lyophilized material was

Table 2
Indicator properties and calibration

Indicator	Medium	pH range	Equation	R^2
Thymol blue	0.5 M phosphate buffer	1.53–2.53	$y = 2.04 + 1.10x$[a]	0.999
Thymol blue	0.5 M phosphate buffer + 25% (v/v) IPA	1.68–2.98	$y = 2.20 + 1.41x$[a]	0.999
Bromophenol blue	0.05 M citrate buffer	2.83–4.90	$y = 3.56 + 0.904x$[a]	0.998
Bromophenol blue	0.05 M citrate buffer + 25% (v/v) IPA	3.21–5.26	$y = 3.88 + 1.462x$[a]	0.991

[a] y = solution pH, $x = \log_{10}$(signal ratio).

gently ground with a mortar and pestle in a glove box under nitrogen flow and was placed in a desiccator over anhydrous calcium sulfate (Drierite).

2.2.2. Spectra of the indicators in solution

The visible spectra for all samples were recorded using a Cary 100 Bio Spectrophotometer (Varian Inc., Mulgrave, Victoria, Australia) equipped with a diffuse reflectance accessory (model DRA-CA-301, Labsphere, North Sutton, NH, USA). Measurements were conducted over a wavelength range of 350–700 nm. The calibration curves were obtained by measuring the spectra of pH adjusted indicator solutions (using phosphate or citrate buffers) containing either 0.0% or 25% (v/v) isopropyl alcohol (IPA). Isopropyl alcohol was selected as a model cosolvent to adjust the polarity, although other cosolvents might be used and will be investigated in future work. The concentration of the indicators used was 15 μg/ml. A buffer (with 0.0% or 25%, v/v) IPA and within the same pH range) was used for baseline correction (blank). The correlation between the solution pH and the log of the peak height ratio was then determined; the peak height ratio was defined as the basic peak maximum signal divided by the acidic peak maximum signal.

2.2.3. Spectra of the indicators in lyophiles

The diffuse reflectance spectra of the lyophiles were measured using a powder sample holder containing a quartz window. The approximate fill weight was 1.2 G and the reflectance spectra of the lyophiles without the indicators were used for baseline correction. The relationships between the solution pH and the log of the peak height ratio were used to calculate the solid-state acidity of the lyophiles from their measured peak ratios. The ratio of extinction coefficients of the deprotonated to the protonated forms of bromophenol blue indicator in solutions and in lyophiles were determined in our laboratory and were not significantly different. However, it was not possible to determine that ratio for thymol blue indicator since the pK_a is less than 2, therefore an assumption was made that the absorptivities in solution and in lyophile are the same.

2.2.4. Sucrose inversion kinetics

2.2.4.1. Assay method. Glucose assay was performed by the Trinder method using a glucose determination kit (Diagnostic Chemicals Ltd., Charlottetown, Prince Edward Island, Canada). During analysis, 300 μl of each solution were taken and added to 5 ml of the reagent solution. The reagent solution was used as a blank and the solutions were maintained at room temperature for 15 min to reach the colorimetric endpoint. Solutions were transferred to 1.4-ml quartz cuvette and the absorbance was measured at 505 nm. Based on the measured glucose concentration, the unhydrolyzed sucrose concentration in the prelyo solutions and in the lyophiles were calculated.

2.2.4.2. Kinetic studies in solution. The increase in glucose concentration with time at various buffer concentrations, various sucrose concentrations and in the prelyo solutions described in Table 1 was followed by using the colorimetric method described above. Solutions were freshly prepared and maintained at 60 °C in a temperature-controlled oven. Solutions were sampled at time zero and at predetermined time intervals. Samples were analyzed immediately using the Trinder method as described above.

2.2.4.3. Kinetic studies in lyophiles. At the end of the freeze-drying cycle, the lyophiles were gently ground with a mortar and pestle in a glove box under nitrogen flow and were placed in desiccators over anhydrous calcium sulfate (Drierite). The lyophiles were

Table 3
The Hammett acidity function of the lyophiles and the reaction rate constants of the prelyo solutions and the lyophiles

Citric acid:Na citrate weight ratio	Prelyo solutions				Lyophiles		
	Buffer concentration (mM)	pH	NaCl (mg/ml)	Reaction rate constant (h^{-1})[a]	Reaction rate constant ($\times 10^{-5}\ h^{-1}$)[a]	Hammett acidity[b]	Hammett acidity[c]
3.96	1	3.25	0.00	0.007	2.21	2.31[TB]	2.55[TB]
3.96	1	3.25	1.25	0.009	7.76	2.12[TB]	2.31[TB]
3.96	10	2.78	1.15	0.057	10.27	2.01[TB]	2.16[TB]
3.96	50	2.59	0.72	0.135	9.41	2.01[TB]	2.16[TB]
1.96	1	3.34	0.00	0.009	1.29	2.48[TB]	2.76[TB]
1.96	1	3.35	1.24	0.008	5.39	2.26[TB]	2.49[TB]
1.96	10	2.90	1.08	0.047	6.38	2.22[TB]	2.43[TB]
1.96	50	2.79	0.34	0.073	5.48	2.23[TB]	2.44[TB]
1.21	1	3.32	0.00	0.007	1.21	2.85[BB]	2.73[BB]
1.21	1	3.31	1.24	0.009	4.17	2.84[BB]	2.71[BB]
1.21	10	2.92	1.01	0.027	4.58	2.84[BB]	2.72[BB]
1.21	50	2.85	0.00	0.047	3.34	2.79[BB]	2.64[BB]

[a] Obtained by fitting the experimental data to Eq. (3).
[b] The Hammett acidity was calculated using the aqueous calibration plots.
[c] The Hammett acidity was calculated using the 25% IPA calibration plots.
[TB] Thymol blue was used as an indicator.
[BB] Bromophenol blue was used as an indicator.

then maintained at 60 °C in a temperature controlled convective oven. Weighed amounts of the lyophiles (250–500 mg) were taken at time zero and at predetermined time intervals and were placed in 5-ml volumetric flasks and 50 mM phosphate buffer (pH 6.5) was added to each flask to obtain a final volume of 5 ml. Samples were then analyzed using the Trinder kit and the method described above. No significant degradation during the analysis occurred due to the raise in the pH and the immediate analysis of the samples.

2.2.5. X-ray powder diffraction

All X-ray powder diffraction patterns of the lyophiles were collected by utilizing a Siemens X-ray diffractometer (Model D5005, Siemens). The radiation was generated by Cu Kα radiation filter at 45 kV and 40 mM. The samples were scanned from 5° to 45° 2θ, with a step size of 0.05 2θ and dwell time of 1.0 s. In all cases initial and reacted samples exhibited no diffraction peaks and had the halo characteristic of a completely amorphous phase.

2.2.6. Water content

At the end of the lyophilization, a weighed amount of the lyophile (~50 mg) was taken and a weighed amount of anhydrous methanol (~8 g) was added to it. The lyophile and the methanol were mixed very well and then a known weight of the solution was injected into the titration vessel of a Karl Fischer titremetry. Based on the amount of the lyophile, the quantity of the added methanol and the water content in the methanol blank, the water content of the lyophile was calculated. Water content (in the lyophiles) was also determined at the end of the kinetic study. At the end of the lyophilization, the average water content of lyophiles was 1.4 ± 0.2% and it did not change substantially during the time course of the experiments.

2.2.7. Differential scanning calorimetry (DSC)

A DSC with a refrigerated cooling accessory was used. The instrument was calibrated with indium. About 8–10 mg of the lyophile were packed in the aluminum pans and crimped. The samples were heated to 130 °C at 10 °C/min, cooled back to room temperature and reheated to 140 °C under a stream of nitrogen. The first heating ensured removal of history. The glass transition temperatures (T_g) were determined from the first and the second runs. The T_g values were obtained from the extrapolated onset of the endothermic step transition in the heating curve.

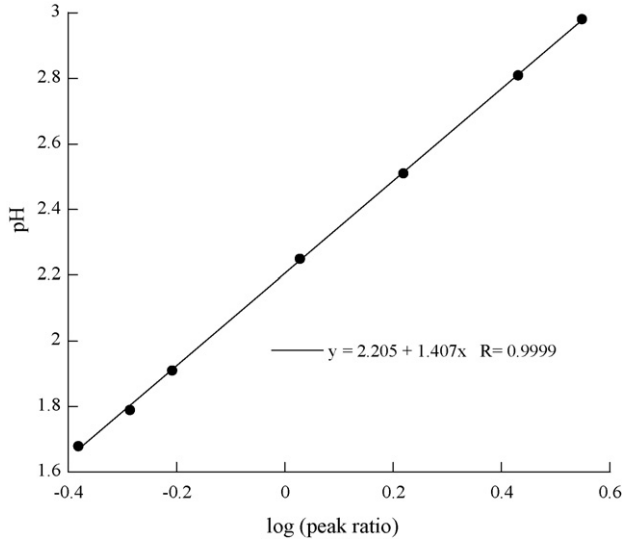

Fig. 2. Solution pH vs. log(peak ratio) plot for thymol blue in water–isopropyl alcohol (25%, v/v) mixtures.

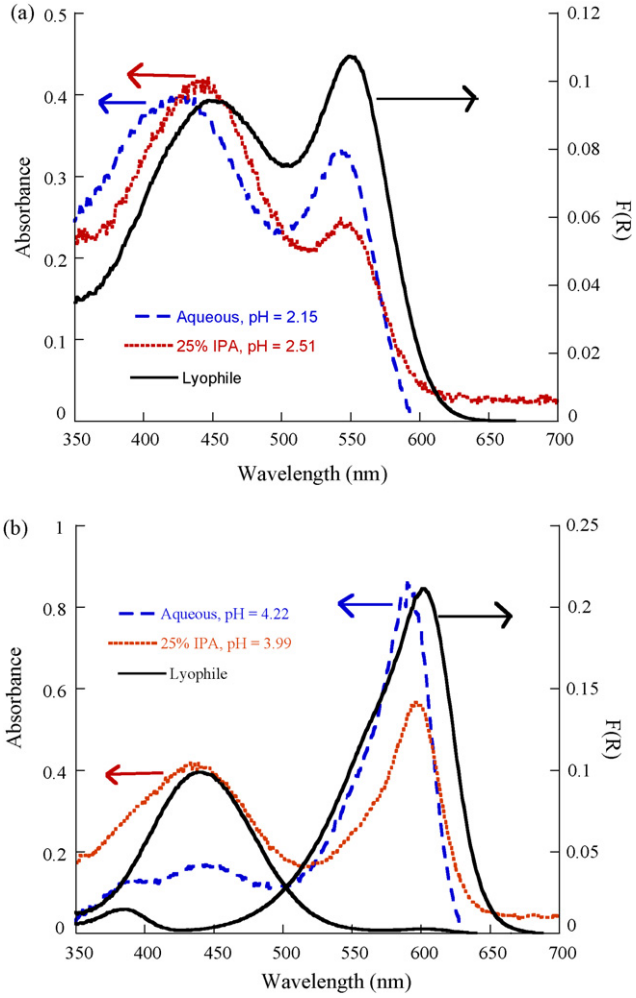

Fig. 3. The spectra of (a) thymol blue and (b) bromophenol blue in aqueous and in 25% IPA media were overlaid on the diffuse reflectance spectra of the lyophile.

3. Results and discussion

3.1. The glass transition temperatures

Table 1 lists the various samples used in this study, including the citric acid:sodium citrate weight ratio, initial solution pH, sodium chloride added to adjust the ionic strength and the glass transition temperatures measured from the DSC runs. The results clearly show a reduction in T_g values with increasing citric acid:sodium citrate weight ratio for the same buffer concentration. This result is expected, since citric acid has the lowest T_g value (~11 °C) of all components followed by mono sodium citrate (Lu and Zografi, 1998; Li et al., 2002) (~69 °C). To evaluate the ideality of the mixtures, the Fox equation (Li et al., 2002) was applied

$$\frac{1}{T_g} = \frac{w_1}{T_{g_1}} + \frac{w_2}{T_{g_2}} + \frac{w_3}{T_{g_3}} + \frac{w_4}{T_{g_4}} \quad (2)$$

where w_1, w_2, w_3 and w_4 represent the weight fractions of components with corresponding T_g values of T_{g_1}, T_{g_2}, T_{g_3} and T_{g_4}. The T_g for lactose (Hancock and Zografi, 1994) is 110 °C while the T_g for sucrose (Hancock and Zografi, 1994) is 74 °C.

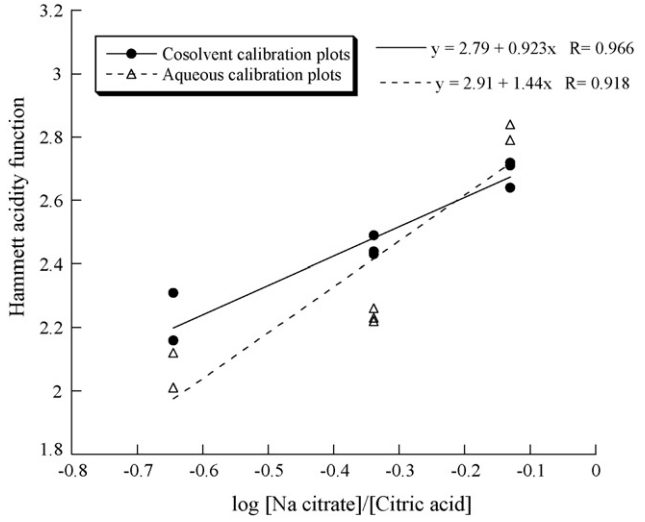

Fig. 4. Hammett acidity of the lyophiles as a function of log(Na citrate/[citric acid) molar ratio. The Hammett acidity was calculated using the aqueous and the cosolvent calibration plots.

In general, similar pattern was observed between the experimental and the calculated values. Equal density of the components was also assumed by Fox equation, and this might have added to the difference.

3.2. Calibration plots and solid-state acidity measurements

The UV–vis spectra of thymol blue and bromophenol blue were collected over a range of solution pH values containing 0.0% and 25% (v/v) isopropyl alcohol. IPA was selected as a cosolvent to "mimic" the spectral properties of the indicators because of changes in the media properties, e.g., polarity, as a result of water removal. Typical spectra of bromophenol blue in aqueous and in cosolvent media are shown in Fig. 1. pH vs. peak ratio calibration curves were constructed and a typical plot is shown in Fig. 2. The regression relationships obtained from these curves, their effective pH range and other relevant details are presented in Table 2. These relationships were used to calculate the Hammett acidity in the lyophiles. More specifically, the x = log(peak ratio) was determined in the lyophiles,

Table 4
Peak positions and the media of the indicators employed in this study

Indicator and medium	λ_{max} (nm)	
	Acidic	Basic
Thymol blue (aqueous)	543	430
Thymol blue (25%, v/v IPA)	549	447
Thymol blue (solid state)	549	447
Bromophenol blue (aqueous)	444	590
Bromophenol blue (25%, v/v IPA)	433, 439	596
Bromophenol blue (solid state)	440	602

and the Hammett acidity function was calculated using the equations in Table 2. The prepared lyophiles, the pH of their prelyo solutions and their Hammett acidities (calculated using aqueous and cosolvent calibration plots) are summarized in Table 3. It is obvious from Table 3 that the Hammett acidities determined using the aqueous and the cosolvent calibration plots are different. This difference may be associated with changes in spectral properties of the indicators because of the decrease in medium polarity as water is removed. Therefore, it could be expected that a mixed solvent (e.g., IPA solution) may provide a more similar environment to lyophiles as related to aqueous solutions. Previous investigators (Mukerjee and Cardinal, 1978; Cardinal and Mukerjee, 1978; Alkhamis et al., 2003) used spectroscopy to establish the site of solubilization in micellar systems. UV–vis spectroscopy was also used in this study to determine the environment of the indicators in the lyophiles as compared with aqueous solution and 25% IPA solution. If the environment in the solid state is similar to the aqueous medium, then the spectra in the aqueous medium and in the solid state should be similar. However, if the environment in the solid state is similar to the cosolvent system, then the spectra in the cosolvent system and in the solid state should be similar. The spectra of the two indicators in aqueous and in semipolar media (i.e. cosolvent) were overlaid on the diffuse reflectance spectra of the lyophiles in Fig. 3. The peak positions of these indicators (in different medias) are shown in Table 4. It is obvious from Fig. 3 and Table 4 that the environment in the solid state resembles the cosolvent system more than the aqueous medium. This result indicates that using cosolvents in the calibration curves might provide a better estimate for the Hammett acidity than the aqueous medium. An attempt was also made to correlate the Hammett acidity values of

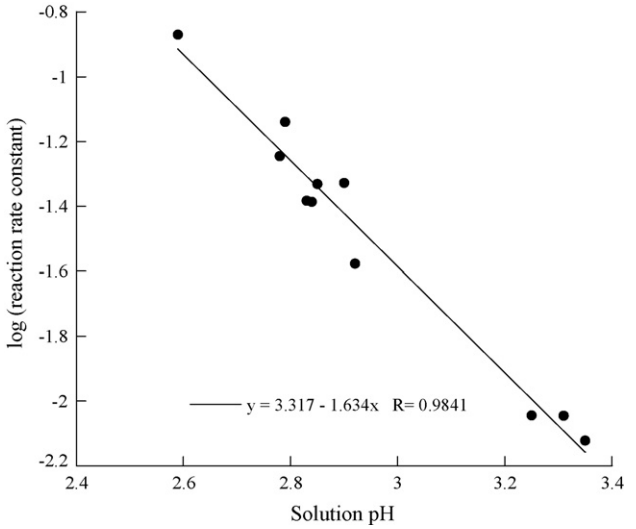

Fig. 5. pH–rate profile for the acid-catalyzed sucrose hydrolysis to glucose in the prelyo solutions.

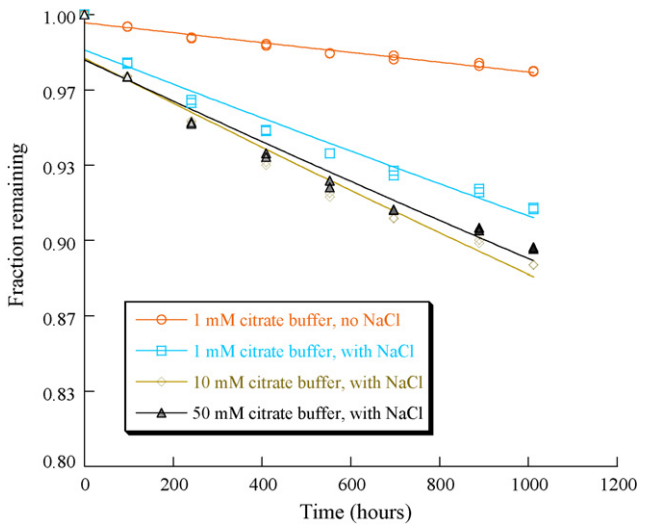

Fig. 6. Sucrose hydrolysis in the freeze-dried samples (citric acid:sodium citrate weight ratio = 3.96).

the lyophiles obtained from the aqueous and the cosolvent calibration plots (using both indicators) to the log(Na citrate/citric acid) molar ratio used in buffer preparation (Fig. 4). Reasonable correlation was obtained between the Hammett acidity function (obtained from the cosolvent calibration plots) and the log(Na citrate/citric acid) molar ratio. The slope is close to one and the intercept is close to the pK_{a_1} of citrate buffer in solution ($pK_{a_1} = 3.128$). However, when the aqueous calibration plots were used, correlations between the log(Na citrate/citric acid) molar ratio and the Hammett acidity function were less satisfactory. This result also indicated that using cosolvents in the calibration curves might provide a better estimate for the Hammett acidity than the aqueous medium. Sucrose inversion studies (discussed below) also supported this conclusion.

3.3. Sucrose inversion kinetics in the prelyo solutions and in the lyophiles

The kinetic curves for the loss of sucrose with time in solution (not shown) agree with what was previously published in the literature (Pentar et al., 2002); a first-order rate constant for the degradation of sucrose in solution was observed. The reaction rate constants for the loss of sucrose in the prelyo solutions are shown in Table 3. The prelyo solutions showed specific acid catalysis, while general catalysis due to the citrate buffer was insignificant. Yukov (1965) developed an empirical equation to describe the pseudo-first-order rate constants for sucrose degradation in solution:

$$\log k_a = 16.91 + \log(d - c) - \left(\frac{5670}{T}\right) - \text{pH} \quad (3)$$

where c is the sucrose concentration in g/ml, d is the density of solution in g/ml, T is the temperature in Kelvin and k_a is the reaction rate constant in min^{-1}. This equation was shown to describe very well the experimental results obtained in this study, even though an assumption was made that the density of the solution is similar to the density of water (1 g/ml). As an example, for a measured pH of 2.59 the predicted k_a from Eq. (3) was 0.117 h^{-1}, while the experimental value obtained in our laboratory was 0.135 h^{-1}. The relationship between the reaction rate constant (in solution) and the pH of the prelyo solutions is shown in Fig. 5. This figure clearly shows that there is a linear relationship between the log(reaction rate constant) and the pH of the prelyo solutions, which agrees with what was previously described in the literature (Yukov, 1965).

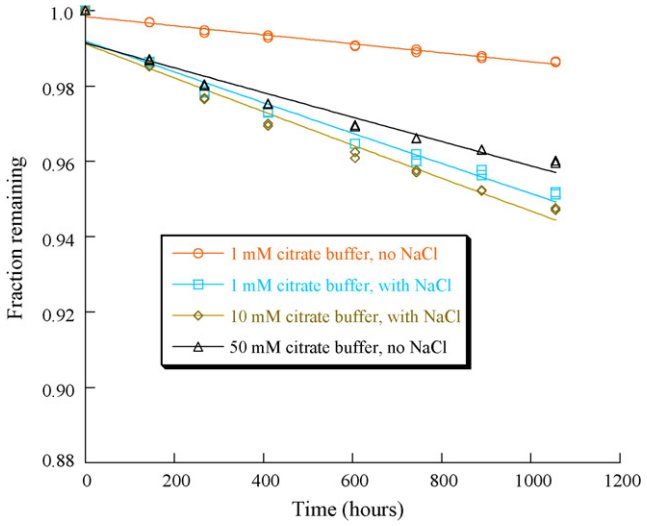

Fig. 8. Sucrose hydrolysis in the freeze-dried samples (citric acid:sodium citrate weight ratio = 1.21).

The kinetic curves for the loss of sucrose with time in the lyophiles are shown in Figs. 6–8. The reaction rate constants for the loss of sucrose are also shown in Table 3. The results clearly show that increasing the ionic strength (by addition of NaCl) had a significant effect on increasing sucrose inversion in the lyophiles. This effect was insignificant in solution since the ionic strength was less than 0.022 M. The effect of ionic strength on sucrose inversion in the lyophiles agrees also with what was previously published in the literature regarding the effect of ionic strength on sucrose inversion in solution (Dordick and Clarke, 1979). Figs. 6–8 clearly show that the ionic strength plays an important role in sucrose degradation in the lyophiles and that for a constant ionic strength the 1 mM, 10 mM and 50 mM buffer show similar sucrose degradation. The similarity in sucrose degradation for the different buffer concentrations agrees very well with the results obtained from the Hammett acidity function using the probe indicators; the 1 mM citrate buffer is capable of adjusting the acidity in the solid state although its

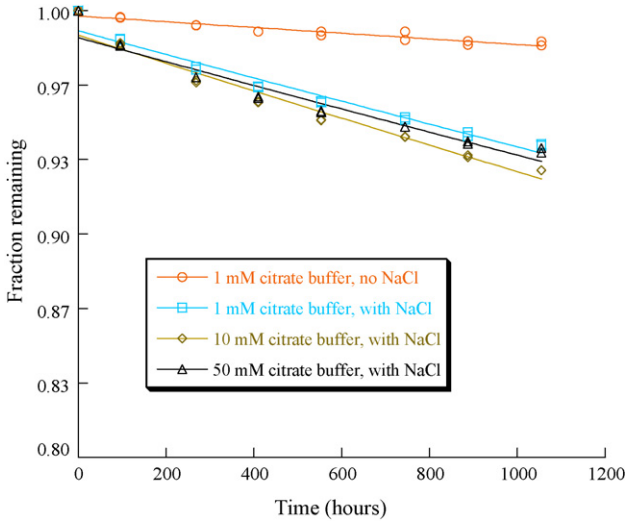

Fig. 7. Sucrose hydrolysis in the freeze-dried samples (citric acid:sodium citrate weight ratio = 1.96).

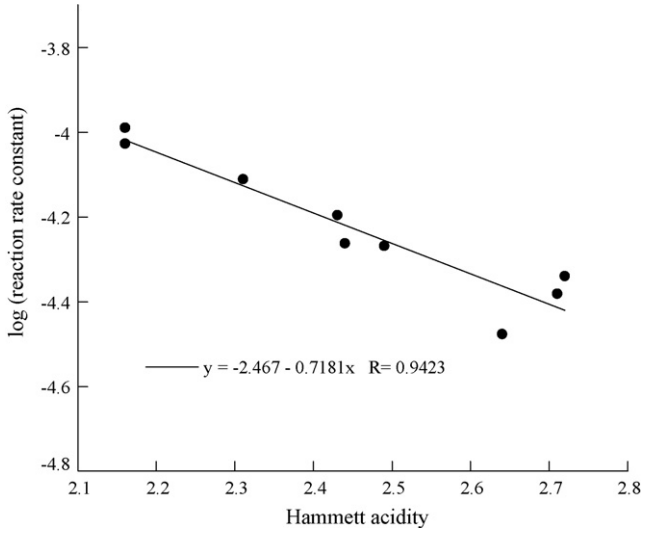

Fig. 9. Hammett acidity–rate profile for the acid-catalyzed sucrose hydrolysis to glucose (Hammett acidity was calculated using the cosolvent method).

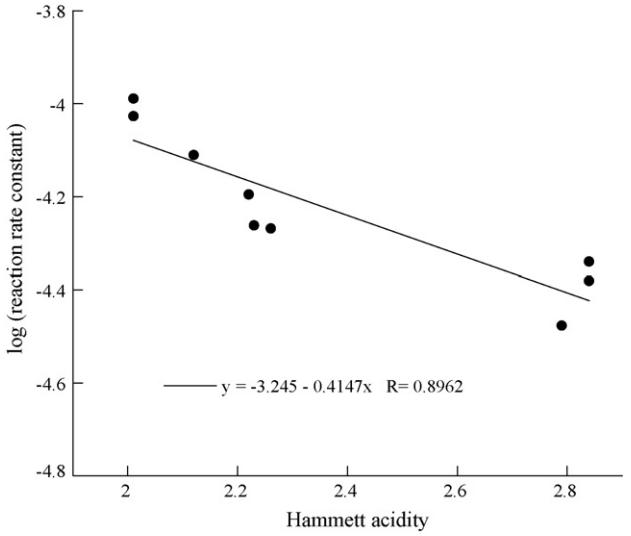

Fig. 10. Hammett acidity–rate profile for the acid-catalyzed sucrose hydrolysis to glucose (Hammett acidity was calculated using the aqueous method).

buffer capacity is extremely low in solution. First-order reaction rate constants of the lyophiles were determined from Figs. 6–8 and the following equation:

$$C = C_0 \times e^{-kt} \quad (4)$$

where C, C_0, t and k are the remaining concentration, the initial concentration, the time and the reaction rate constant, respectively.

An attempt was also made to correlate sucrose degradation to the Hammett acidity function using the cosolvent and the aqueous media in the calibration plots. This is shown in Figs. 9 and 10. Good correlation was obtained using the cosolvent method. However, the results obtained using the aqueous method, were less satisfactory. (This decision is based on the R values and the slopes, which should be close to the theoretical value of -1.)

4. Conclusions

This study has shown that Hammett acidity function provided good correlations with the rate of acid-catalyzed reaction, sucrose inversion, in amorphous lyophiles. The use of cosolvents (in the calibration plots) can provide a better estimate for the solid state acidity than aqueous medium. It is further shown that the solid-state acidity depends mainly on the molar ratio of the salt and the acid used in buffer preparation and not on the initial pH of the solution. The degradation of sucrose in the lyophiles is extremely sensitive to the solid-state acidity and the ionic strength. The Hammett acidity–rate profile for sucrose degradation in the lyophiles was also obtained, and it showed similarity to the pH–rate profile in solution (specific acid catalysis).

Acknowledgments

The author would like to thank Prof. Raj Suryanarayanan from the University of Minnesota and Dr. Evgenyi Shalaev from Pfizer Inc. for their help.

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